Safety communication
Additional Monitoring
Signal Management

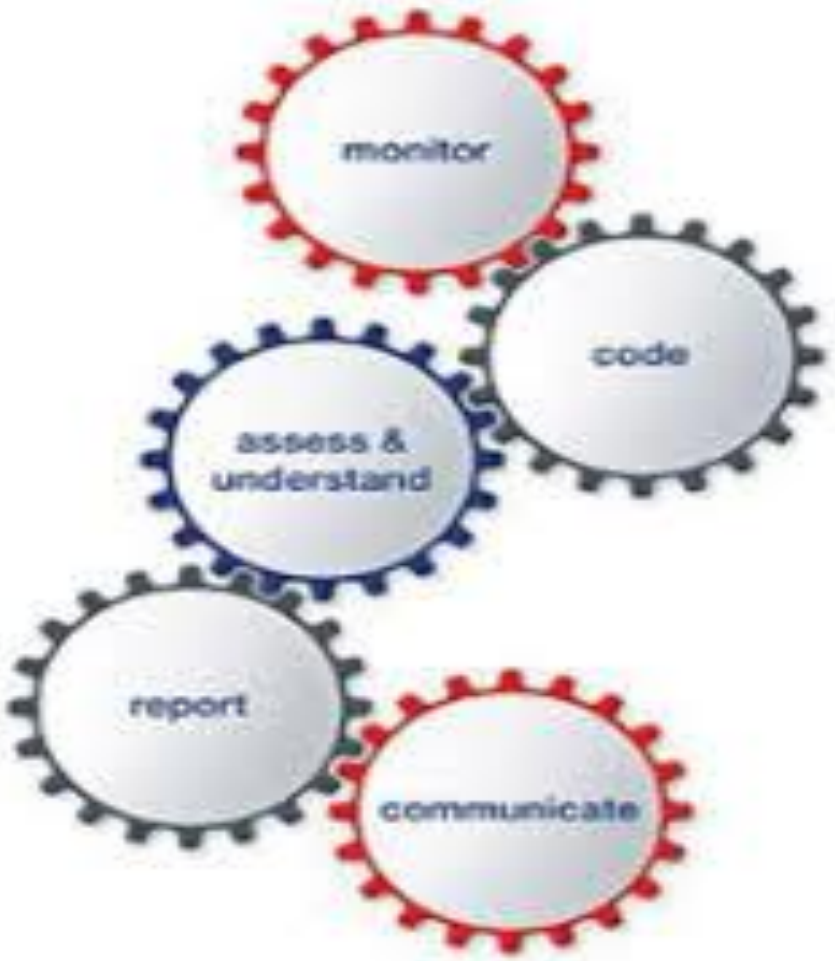
Pharmacovigilance

What is Pharmacovigilance ?

- Pharmakon (Greek) = Medicinal Substances
- Vigilia (Latin) = To keep watch

WHO Definition

- The science & activities relating to the detection, assessment, understanding & prevention of adverse effects or any other drug related problems



Signal Management

The Report of the Council for International Organizations of Medical Sciences defines a **signal** *as* information that arises from one or multiple sources (including observations and experiments), which suggests a **new** potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to **justify verificatory action.**

SO = only new information related to adverse effects will be considered.

Signal Management

In order to suggest a new potentially causal association or a new aspect of a known association, any signal should be **validated** taking into account other relevant sources of information.

SO = only new information related to adverse effects will be considered.

Signal Management

The signal management process can be defined as the **set of activities** performed to determine whether, based on

- an examination of individual case safety reports (ICSRs),
- aggregated data from active surveillance systems or studies,
- literature information or other data sources,
- there are new risks associated with an active substance or a medicinal product or whether known risks have changed.

The signal management process include all steps from initial signal **detection**; through their **validation** and **confirmation**; **analysis** and **prioritization**; and signal **assessment** to recommending action, as well as the **tracking** of the steps taken and of any recommendations made.

Signal Management

The signal management process concerns **all stakeholders** involved in the safety monitoring of medicinal products including patients, healthcare professionals, marketing authorization holders (MAHs), regulatory authorities, scientific committees.

Whereas the **ADRs** database will be a **major** source of pharmacovigilance information, the signal management process covers signals arising from any source., only signals related to an adverse reaction shall be considered.

Signal Management

Sources of data and information

The sources for identifying new signals are **diverse**. They potentially include all scientific information concerning the use of medicinal products including quality, non-clinical, clinical, pharmacovigilance and pharmacoepidemiological data.

Specific sources for signals include spontaneous adverse drug reaction (ADR) reporting systems, active surveillance systems, non-interventional studies, clinical trials, scientific literature and other sources of information.

Signal Management

Sources of data and information

Signals from spontaneous reports may be detected from monitoring of individual case safety reports (ICSRs), ADR databases, articles from the scientific literature or review of information provided by marketing authorization holders in the context of **regulatory procedures** (e.g. variations, renewals, post-authorization commitments, periodic safety update reports (PSURs), Risk Management Plan (RMP) updates or from other activities related to the on-going benefit-risk monitoring of medicinal products.

Signal Management

Sources of data and information

Spontaneous reports of ADRs may also be notified to poison centers, teratology information services, vaccine surveillance programmes, reporting systems established by marketing authorization holders, and any other structured and organized data collection schemes allowing patients and healthcare professionals to report suspected adverse reactions related to medicinal products. National medicines authorities should liaise with other institutions or organizations managing such reporting system so as to be informed of these suspected adverse reactions.

Signal Management

Sources of data and information

Due to the increase in volume of spontaneous reports of (ADRs), the introduction of electronic safety reporting by patients and healthcare professionals and the mandatory electronic submission of case reports from marketing authorization holders to medicines authorities in Arab Countries, signal detection is now **increasingly** based on periodic monitoring of **large databases** of ADRs reports.

Signal Management

Sources of data and information

Signals may arise from a wide range of different study types, including quality, non-clinical, interventional and non-interventional studies, systematic reviews and meta-analyses. Interventional trials and observational studies may, by design, recruit and follow-up a defined population of subjects who may experience ADRs. **Review of aggregated data and statistical analyses** may also point to an elevated risk of an adverse event to be further investigated as a signal.

Published results of relevant studies should be identified by marketing authorization holders by screening the scientific literature.

Signal Management

Sources of data and information

Marketing authorization holders should **regularly screen** internet or digital media under their management or responsibility for potential reports of suspected ADRs, which may characterize a new signal. Marketing authorization holders and medicines authorities in Arab Countries should seek further information related to suspected ADRs they become aware of from any source. Suspected serious ADRs should be confirmed if possible through other data sources such as ―National Pharmacovigilance and Safety reports database‖ if accessible to MAHs (**EPVC**)

Signal Management

The signal management process

Signal Detection

Signal Validation

Signal Analysis and Prioritization

Signal Assessment

Recommendation for action

Exchange of information

Signal Management

The signal management process

- **Although these steps generally follow a logical sequence, the wide range of sources of information available for signal detection may require some flexibility in the conduct of signal management e.g.:**

  - when signal detection is primarily based on a review of individual case safety reports (ICSRs), this activity may include validation and preliminary prioritization of any detected signal;
  - when a signal is detected from results of a study, it is generally not possible or practical to assess each individual case, and validation may require collection of additional data;
  - recommendation for action (followed by decision in accordance with the applicable legislation) and exchange of information are components to be considered at every step of the process.

Signal Management

Methodology for signal detection

As a general principle, **signal detection** should follow a recognized methodology, which may vary depending on the type of medicinal product it is intended to cover. Vaccines may for example require other methodological strategies.

The detection of signals shall be based on a **multidisciplinary approach**. Signal detection within the ―National Pharmacovigilance and Safety reports database‖ or MAH-specific ADRs database shall be complemented by **statistical analysis** where appropriate.

Signal Management

Methodology for signal detection

Whichever methods are employed for the detection of signals, the same **principles** should apply, namely

- the method used should be appropriate for the data set; for example, the use of complex statistical tools may not be appropriate for smaller data sets;
- data from all appropriate sources should be considered;
- systems should be in place to ensure the quality of the signal detection activity;
- any outputs from a review of cumulative data should be assessed by an appropriately qualified person in a timely manner;
- the process should be adequately documented, including the rationale for the method and periodicity of the signal detection activity.

Signal Management

Methodology for signal detection

Detection of signals may be performed based on a review of ICSRs, from statistical analyses in large databases, or from a combination of both.

Review of individual case safety reports

Even a single report of a serious or severe adverse reaction (for example, one case of toxic epidermal necrolysis, aplastic anaemia or liver transplant, or serious adverse event concerning children or pregnancy) may be sufficient to raise a signal and to take further action.

Signal Management

Methodology for signal detection

Detection of signals may be performed based on a review of ICSRs, from statistical analyses in large databases, or from a combination of both.

Review of individual case safety reports

A review of ICSRs for this purpose should consider the number of cases (after exclusion of duplicates), the patient's demographics (including age and gender), the suspected medicinal product (including dose administered, formulation) and the suspected adverse reaction (including signs and symptoms), the temporal association, the clinical outcome in relation to drug continuation or discontinuation (i.e. de-challenge / re-challenge information).

Signal Management

Methodology for signal detection

Detection of signals may be performed based on a review of ICSRs, from statistical analyses in large databases, or from a combination of both.

Review of individual case safety reports

An assessment of causality of a suspected association should also consider, the presence of potential alternative causes including other concomitant medications, the underlying disease, the reporter's evaluation of causality and the plausibility of a biological and pharmacological relationship.

Signal Management

Methodology for signal detection

Detection of signals may be performed based on a review of ICSRs, from statistical analyses in large databases, or from a combination of both.

Statistical analyses

Signal detection is now increasingly based on a regular periodic monitoring of large databases of reports of ADRs. Such databases allow generation of statistical reports presenting information on adverse reactions received over a defined time period for defined active substances or medicinal products. Various methods have been developed to identify statistics of disproportionate reporting, i.e. higher reporting than expected for an suspected adverse reaction for an active substance/medicinal product of interest compared to all other active substances/medicinal products in the database.

Signal Management

Methodology for signal detection

Detection of signals may be performed based on a review of ICSRs, from statistical analyses in large databases, or from a combination of both.

Statistical analyses

Use of statistical tools may not be appropriate in all situations. The size of the data set, the completeness of the available information and the severity of the adverse reaction(s) should be taken into account when considering the use of statistical methods and the selection of criteria for the detection of signals.

Signal Management

Methodology for signal detection

Detection of signals may be performed based on a review of ICSRs, from statistical analyses in large databases, or from a combination of both.

Statistical analyses

The periodicity at which statistical reports should be generated and reviewed may vary according to the active substance/medicinal product, its indication and any known potential or identified risks. Some active substances/medicinal products may also be subject to an increased frequency of data monitoring. The duration for this increased frequency of monitoring may also vary and be flexible with the accumulation of knowledge of the risk profile associated with the use of the concerned active substance/medicinal product.

Signal Management

Methodology for signal detection

Detection of signals may be performed based on a review of ICSRs, from statistical analyses in large databases, or from a combination of both.

Combination of statistical methods and review of individual case safety reports

Statistical reports may be designed to provide tools for identifying suspected adverse reactions that meet pre-defined criteria of frequency, severity, clinical importance, novelty or statistical association. Such filtering tools may facilitate the selection of ICSRs to be reviewed as a first step. The thresholds used in this filtering process (for example, at least 3 cases reported) may vary according to the extent of usage of medicinal products and thus the potential public health impact.

Signal Management

Methodology for signal detection

Detection of signals may be performed based on a review of ICSRs, from statistical analyses in large databases, or from a combination of both.

Combination of statistical methods and review of individual case safety reports

Irrespective of the statistical method used, where statistical reports are used to automate the screening of a database, signal detection should always involve clinical judgement and the corresponding ICSRs should be individually reviewed, considering their clinical relevance

The statistical method should therefore be a supporting tool in the whole process of signal detection and subsequent validation.

Signal Management

Methodology for signal validation

Signal validation is the process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association or a new aspect of a known association, and therefore justifies further analysis.

To validate a signal the following should be taken into account

Clinical relevance

Previous awareness

Availability of other relevant sources of information providing a richer set of data on the same association

Signal Management

Methodology for signal validation

To validate a signal the following should be taken into account

Clinical relevance

Strength of evidence for a causal effect (e.g. number of reports, exposure, temporal association, plausible mechanism, de/re-challenge, alternative explanation/confounders)

Seriousness and severity of the reaction and its outcome

Novelty of the reaction (e.g. new and serious adverse reactions)

Drug drug interactions

Reactions occurring in special populations

Signal Management

Methodology for signal validation

To validate a signal the following should be taken into account

Previous awareness

The extent to which information is already included in the summary of product characteristics (SmPC) or patient leaflet.

Whether the association has already been assessed in a PSUR or RMP, or was discussed at the level of a scientific committee or has been subject to a regulatory procedure.

In principle only a new signal for which there is no previous awareness should be validated. However, an already known association may give rise to a new signal if its apparent frequency of reporting, its duration, its severity or a change in the previously reported outcome (such as new fatality) suggests new information as compared with the information included in the SmPC or previously assessed by the competent authority.

Signal Management

Methodology for signal validation

To validate a signal the following should be taken into account

Availability of other relevant sources of information providing a richer set of data on the same association

Literature findings regarding similar cases

Experimental findings or biological mechanisms

Screening of larger database

Signal Management

Methodology for signal validation

Signals for which the validity is not confirmed may deserve special attention in subsequent analyses i.e. it may be appropriate to continue to monitor the potential signal until there is enough evidence to confirm the signal. For example, there might be an inadequate case documentation or a supporting evidence of a causal association only in some of the ICSRs. In such scenarios, new cases of the same adverse reaction or follow-up reports of previously received cases should be reviewed at appropriate time intervals to ensure that all relevant cases are considered.

Signal Management

Methodology for signal validation

Marketing authorisation holders and national medicines authorities should establish tracking systems to capture the outcome of the validation of signals including the reasons why signals were not validated as well as information that would facilitate further retrieval of ICSRs and validation of signals.

Signal Management

Methodology for signal analysis and prioritization

A key element of the signal management process is to promptly identify validated signals with important public health impact or that may significantly affect the benefit-risk profile of the medicinal product in treated patients. These signals require urgent attention and need to be prioritised for further management without delay.

Signal Management

Methodology for signal analysis and prioritization

This prioritization process should consider:

- impact on patients depending on the severity, reversibility, potential for prevention and clinical outcome of the association
- consequences of treatment discontinuation on the disease and the availability other therapeutic options
- strength and consistency of the evidence supporting an association, e.g., biological plausibility, a high number of cases reported in a short period of time, the measure of
- disproportionality of reporting and rapid increase of that measure over time and identification of the signal in different settings (e.g. general practice and hospital settings), data sources or countries

Signal Management

Methodology for signal analysis and prioritization

This prioritization process should consider:

- clinical context (e.g. whether the association suggest a clinical syndrome that may include other reactions)
- the public health impact, including the extent of utilisation of the product in the general population and in special populations (e.g. pregnant women, children or the elderly) and the patterns of medicinal product utilisation (e.g. off-label use or misuse). The public health impact may include an estimation of the number of patients that may be affected by an adverse reaction and this number could be considered in relation to the size of the general population, the population with the target disease and the treated population;

Signal Management

Methodology for signal analysis and prioritization

This prioritization process should consider:

- increased frequency or severity of a known adverse reaction
- novelty of the suspected adverse reaction, e.g. when an unknown suspected adverse reaction occurs shortly after the marketing of a new medicinal product
- if a marketing authorisation application for a new active substance is still under evaluation

Signal Management

Methodology for signal analysis and prioritization

In some circumstances, priority can also be given to signals identified for medicinal products or events with potential high media and pharmacovigilance stakeholder interest in order to communicate the result to the public and healthcare professionals as early as possible.

The outcome of signal prioritisation should include a recommendation of the time frame for the management of the signal.

The outcome of the signal prioritisation process should be entered in the tracking system, with the justification for the priority attributed.

Signal Management

Methodology for signal assessment

The objective of signal assessment is to further evaluate a validated signal so as to identify the need for additional data collection or for any regulatory action. It consists of an assessment of the available pharmacological, non-clinical and clinical data and information from other sources. This review should be as complete as possible regarding the sources of information, including the application dossier, literature articles, spontaneous reports, expert consultation, and information held by marketing authorisation holders and competent authorities.

Signal Management

Methodology for signal assessment

When information is drawn from a range of sources, the strengths and limitations of each source should be considered in order to assess the contribution they can provide to the overall evaluation of the signal in terms of a recommendation for action. Summarising information from different data sources also requires the choice of an internationally agreed case definition (e.g. Brighton collaboration case definition for vaccines). If no such definition exists, an operational definition should be developed.

Signal Management

Methodology for signal assessment

Signals may need to be assessed at a broader level e.g. at the therapeutic or system organ class level or at the level of a Standardised MedDRA. The search for information to assess the significance of a signal may also need to be extended to other products of the class and to other adverse reactions, such as to other terms linked to a complex disease (e.g. optic neuritis as a possible early sign of multiple sclerosis), to a prior stage of a reaction (e.g. QT prolongation and torsades de pointes) or to clinical complications of the adverse reaction of interest (e.g. dehydration and acute renal failure).

Signal Management

Recommendation for action

Signal assessment results in a recommendation that either no further action is required at this point in time or a further action is needed. Although the recommendation for action normally takes place in a logical sequence after signal assessment based on the extent of the information, the need for action should be considered throughout the signal management process. For example, the first case of an adverse reaction indicating a manufacturing defect may require immediate recall of a product batch.

Signal Management

Recommendation for action

The review of available information at the signal validation or signal prioritisation stages may similarly conclude that the evidence is sufficiently strong to introduce temporary measures. In such situations, it is still necessary to proceed with a formal assessment of the signal to confirm or not the safety issue in order to extend or lift the temporary measures.

Signal Management

Recommendation for action

The recommendation for action may include a request for:

- immediate measures including the possibility of suspending the marketing authorization of the medicinal product;
- additional information to be provided by the marketing authorization holder, e.g. in order to confirm if a conclusion is valid for all indications and patient groups;
- periodic review of the signal, for example through PSURs;
- additional investigations or risk minimization activities;
- an update of the product information through a regulatory procedure;
- conduct of a post-authorisation safety study

Signal Management

Exchange of information

- Information on validated signals, Emerging Safety Issues and the outcome of signal assessments should be exchanged between national medicines authorities and marketing authorization holders.
- Marketing authorization holders should communicate signals that may have implications for public health and the benefit-risk profile of a product immediately to the national medicines authorities as an Emerging Safety Issue and when appropriate this should include proposals for action.

Signal Management

Exchange of information

The outcomes of signal assessment involving new or changed risks and risks that have an impact on the benefit-risk balance of the concerned active substance/medicinal products should be communicated to the public including health care professionals and patients as well as to the concerned marketing authorization holders.

Signal Management

Quality requirements

Tracking

All validation, prioritization, assessment, timelines, decisions, actions, plans, reporting as well as all other key steps should be recorded and tracked systematically. Tracking systems should be used for documentation and should also include signals, for which the validation process conducted was not suggestive of a new potentially causal association, or a new aspect of a known association. All records need to be archived.

Signal Management

Quality requirements

Quality systems and documentation

An essential feature of a signal management system is that it is clearly documented to ensure that the system functions properly and effectively, that the roles, responsibilities and required tasks are standardized, that these tasks are conducted by people with appropriate expertise and are clear to all parties involved and that there is provision for appropriate control and, when needed, improvement of the system.

Through their tracking system, all parties should keep an audit trail of their signal management activities and of the relevant queries and their outcomes, including how signals have been detected, validated, confirmed and assessed.

Signal Management

Quality requirements

Quality systems and documentation

- Documentation may be requested from the marketing authorization holders demonstrating compliance with these provisions and reviewed before and after marketing authorization.
- Staff should be specifically trained in signal management activities in accordance with their roles and responsibilities. The training system and location of the training records should be documented, and curricula vitae and job descriptions should be archived.

Signal Management

Processes for regulatory follow-up in the Arab Countries

The national medicines authority may decide on any or a combination of the following actions

- the marketing authorization holder should submit an *ad-hoc* PSUR
- sponsor a post-authorization study according to an agreed protocol and submit the final results of that study
- the marketing authorization holder should be requested to submit a RMP or an updated RMP
- the marketing authorization holder should take any measures that are required for ensuring the safe and effective use of the medicinal product

Signal Management

Processes for regulatory follow-up in the Arab Countries

The national medicines authority may decide on any or a combination of the following actions

- the marketing authorization should be varied, suspended, revoked or not renewed
- urgent safety restrictions may be imposed
- an inspection should take place in order to verify that the marketing authorization holder for the medicinal product satisfies the pharmacovigilance requirements;
- the medicinal product should be included in the list of medicinal products that are subject to additional monitoring.

Signal Management

Processes for regulatory follow-up in the Arab Countries

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- an inspection should take place in order to verify that the marketing authorization holder for the medicinal product satisfies the pharmacovigilance requirements;
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Great thanks for your kind attendance